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| EXAMINER | |
|---|---|
| FETTEROLF, BRANDON J | |

| ART UNIT | PAPER NUMBER |
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| 1642 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/815,925 | BOSSLET ET AL. | |
| | Examiner | Art Unit | |
| | Brandon J. Fetterolf, PhD | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7,9,12 and 14-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9, 12 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to the Amendment*

The Amendment filed on 09/05/2007 in response to the previous Non-Final Office Action (3/06/2007) is acknowledged and has been entered.

Claims 1-7, 9, 12 and 14-18 are currently pending and under consideration.

### *Priority*

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

**Rejections Withdrawn:**

The rejection of Claim 11 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is withdrawn in view of Applicants canceling claim 11.

The rejection of Claims 1-7, 9-13 and 15-16 under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; laid open to the public on 8/29/1992) in view of Mattes (U.S. Patent 4,859,449; issued 08/1989) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976) is withdrawn in view of Applicants amendments. In particular, the rejection is withdrawn in view of Applicants amendment to the claim to recite that the second portion is not an antibody or antibody fragment. As such, all the claims previously rejected under 35 U.S.C. 103 (a) are withdrawn.

The rejection of Claims 1, 6-7, 9, 12 and 15-16 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 9-11 and 15-16 of U.S. Patent No. 7,060,495 is withdrawn in view of Applicants filing of a Terminal Disclaimer.

**New Rejections Necessitated by Amendment:**

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7, 9, 12 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; laid open to the public on 8/29/1992, of record) in view of Anderson et al. (US 5,135,736) and in further view of Ponpipom et al. (J. Med. Chem. 1981, 24: 1388-1395).

Seemann teaches a fusion protein comprising the general formula huTuMAb-L-β-gluc, wherein huTuMA is a humanized tumor-specific moloclonal antibody or fragment thereof, L is a linker and β-gluc comprises human β-glucuronidase (page 1, 1st paragraph). With regards to huTuMAb, Seemann et al. teach that the huTuMAb includes the antibody binding fragments of anti-CEA BW431/26 monoclonal antibody (page 3, lines 16-23; page 17, lines 25+; and page 23, *Example O*). Moreover, Seemann et al. teach the fusion proteins can be further modified in order to achieve an increased half-life, wherein the fusion proteins are treated with an oxidizing agent which cleaves

the carbohydrate ring, e.g. chemical degradation, which can be further derivatized by reductive animation which generates a new carbohydrate residue (page 4, lines 12-30). Seeman et al. further teach a pharmaceutical composition comprising the fusion protein, wherein the fusion protein was dissolved in tris/HCl buffer (*page 25, Example Q*).

Seemann does not explicitly teach that the fusion proteins or conjugates comprise a targeting agent which is not an antibody or that the conjugates comprise an exposed galactose, mannose, N-acetylglucosamine, lactose, N-acetyllactose, glucose or fucose.

Anderson et al. teach covalently linked complexes for targeting a defined population of cells, comprising a targeting protein or a targeting peptide, a cytotoxic agent and an enhancing moiety (column 1, lines 50-55). With regards to the targeting protein or targeting peptide, the patent teaches that the targeting protein direct the covalently attached cytotoxic agent to a target cell population, such as tumor cells and include, but are not limited to, antibodies, peptides such as bombesin, gastrin releasing peptide, RGD peptides, substance P, nueromedin-B, neuromedin C, and metenkaphalin, and hormones such as EGF, TGF, estradiol, neurotensin, melanocyte stimulating hormone, follicles stimulating hormone, luteinizing hormone and human growth hormone (column 3, lines 28-39).

Ponpimon et al. teach cell-specific ligands for selective drug delivery to tissues and organs, wherein small synthetic glycolipids and glycopeptides comprise D-mannose residues attached to lysine , dilysine and oligolysine backbones (abstract and page 1389, 1st column, 1st full paragraph. In particular, the reference teaches that the concept of exposed sugar residues on glycoproteins serve as determinants for in vivo (i.e., clearacnce) and in vitro (i.e., uptake) recognition (page 1389, 1st column, 1st paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to modify the fusion protein taught by Seemann with a peptide or hormone in view of the teachings of Anderson et al. One would have been motivated to do so because as taught by Anderson et al., antibodies, peptides and hormones are well known in the art to be useful as targeting agents to tumor cells. As such, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the fusion protein taught by Seemann with a peptide or hormone in view of the teachings of Anderson et al, one would achieve a fusion protein capable of targeting a tumor cell.

Moreover, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to modify said fusion protein to further include an exposed sugar moiety such as a mannose in view of the teachings of Ponpimon et al.. One would have been motivated to do so because Ponpimon teaches that the concept of exposed sugar residues on glycoproteins serve as determinants for in vivo (i.e., clearance) and in vitro (i.e., uptake) recognition. As such, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the fusion protein taught by Seemann with a mannose in view of the teachings of Ponpimon , one would achieve a fusion protein having increased clearance from the circulation.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; laid open to the public on 8/29/1992, of recrd) in view of Anderson et al. (US 5,135,736) and Ponpipom et al. (J. Med. Chem. 1981, 24: 1388-1395), as applied above to claims 1-7, 9, 12 and 14-16, further in view of Bosslet (Bosslet et al, Br. J. Cancer 65: 234-238, 1992, of record) and Jahde (Jahde et al, Cancer Res. 52: 6209, 1992; of record).

Seemann in view of Anderson et al. and Ponpipom et al. teach a pharmaceutical composition comprising a recombinantly made fusion glycoprotein comprising a tumor cell binding agent such as a peptide linked to a β-glururonidase having an exposed galactose or mannose residue and a pharmaceutically acceptable carrier such as Tris/HCl buffer..

Seemann in view of Anderson et al. and Ponpipom et al do not explicitly teach that the pharmaceutical composition further comprises an agent that lowers the intracellular pH of tumor cells.

Bosslet teaches that that activity of β-glucuronidase increases at a pH that is lower than physiological pH (page 236, 2nd col.).

Jahde teaches methods of lowering intracellular pH of tumors comprising administering glucose (page 6210, 2nd column, *Results*).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to modify the pharmaceutical composition as taught by Seemann in view of Anderson et al. and Ponpipom et al to include an agent that lowers the intracellular pH of a tumor in view of Bosslet and Jahde. One would have bee motivated to do

so because Bosslet teaches that the activity of β-glucoronidase increases at a pH that is lower that physiological pH and Jahde provides agents which are capable of reducing intracellular pH. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the pharmaceutical composition as taught by Seemann in view of Anderson et al. and Ponpipom et al to include an agent that lowers the intracellular pH of a tumor in view of Bosslet and Jahde, one would achieve a pharmaceutical composition having an agent which increases the enzymatic activity of β-glucuronidase.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; laid open to the public on 8/29/1992, of record) in view of Anderson et al. (US 5,135,736) and Ponpipom et al. (J. Med. Chem. 1981, 24: 1388-1395), as applied above to claims 1-7, 9, 12 and 14-16, further in view of Bagshawe (U.S. Patent 5,632,990; issued 05/1997; filed 12/1990, of record).

Seemann in view of Anderson et al. and Ponpipom et al. teach a pharmaceutical composition comprising a recombinantly made fusion glycoprotein comprising a tumor cell binding agent such as a peptide linked to a β-glururonidase having an exposed galactose or mannose residue and a pharmaceutically acceptable carrier such as Tris/HCl buffer..

Seemann in view of Anderson et al. and Ponpipom et al do not explicitly teach that the pharmaceutical composition further comprises galactose.

Bagshawe teaches the use of galactosylated antibody constructs for the purpose of increased clearance and further teaches methods that comprise the additional use of a substance for blocking glactose residues for the purpose of maintaining a high level of conjugate in the plasma until the galactose receptors are again free to take up the galactosylated conjugate. Bagshawe teaches that asialofetuin binds strongly to galactose receptors but that less immunogenic substances may be identified col. 4, lines 33-41).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to modify the pharmaceutical composition as taught by Seemann in view of Anderson et al. and Ponpipom et al. to include galactose for the purpose of temporarily decreasing clearance of the fusion glycoproteins or conjugates in view of the teachings of Bagshawe et al.. One would have been motivated to do so because Bagshawe et al.

teach the addition of a second substance to block galactose receptors from binding with the galactosylated conjugate. Thus, one of ordinary skill in the art would have had a reasonable expectation of success in using galactose as a substance for temporarily decreasing clearance of the fusion glycoproteins or conjugates because the receptors are galactose receptors.

Therefore, NO claim is allowed

**All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.**

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF